Amendments to the Drawings:

The drawing sheets attached in connection with the above-identified application containing Figures 5, 9 and 13 are being presented as new formal drawing sheets to be substituted for the previously submitted drawing sheets.

Figures 5, 9 and 13 have been amended. Figure 5 has been amended to add the label "Densitometric Intensity" to the y-axis. Support for this change can be found in the specification, e.g., at page 35, line 21, to page 36, line 3.

Figure 9 has been amended to more clearly label the x-axis by repositioning the former x-axis labels.

Figure 13 has been amended to change the x-axis label of the first bar from "Control" to "No peptide", to more clearly indicate that the first bar represents data using no peptide, *i.e.*, peptide at a concentration of zero.

Appended to this amendment are annotated copies of the previous drawing sheets which have been marked to show changes presented in the replacement sheets of the drawings.

REMARKS

Reconsideration of this application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-18 and 24-27 are pending in the application, with claims 1 and 24 being the independent claims. New claims 24-27 are sought to be added by the present amendment. Claims 19-23 are sought to be cancelled by the present amendment without prejudice to or disclaimer of the subject matter therein. Claims 1-18 are currently withdrawn from consideration.

Applicants have amended the specification to correct several typographical and grammatical errors so that the language in the specification conforms to accepted English-language conventions. A substitute specification containing these changes is submitted with the present Amendment. In accordance with 37 C.F.R. § 1.125(c), both a marked-up version of the substitute specification and a clean version (without markings) are provided. The marked-up version of the specification shows all the changes relative to the immediate prior version of the specification.

In accordance with 37 C.F.R. § 1.125(b), Applicants state that the substitute specification being submitted herewith contains no new matter.

Figures 5, 9 and 13 have also been amended. Specifically, Figure 5 has been amended to add the label "Densitometric Intensity" to the y-axis. Support for this change can be found in the specification, e.g., at page 35, line 21, to page 36, line 3. Figure 9 has been amended to more clearly label the x-axis by repositioning the former x-axis labels. Figure 13 has also been amended to change the x-axis label of the first bar from "Control" to "No peptide", to more clearly indicate that the first bar represents data using no peptide, *i.e.*, peptide at a concentration of zero.

New claims 24-27 have also been added. New claims 24-27 are redrafted forms of cancelled claims 19-23. Support for the new claims can be found in original claims 19-23. New claims 24-26 are redrafted forms of cancelled claims 19-21 and 23 and thus recite the invention of Group V, as set out in the Restriction Requirement dated November 29, 2007.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Information Disclosure Statement Issue

The Office states that the non-patent literature documents cited on Applicants' September 26, 2005 Information Disclosure Statement "have not been considered, because the references have not been provided." (Office Action, at page 3, lines 11-15, at paragraph 7.)

To expedite prosecution, Applicants resubmit with the present Amendment and Reply the Information Disclosure Statement submitted on September 26, 2005, along with copies of all cited non-patent references.

II. Objection to the Drawings

The Office objects to Figures 5, 9 and 13 on the basis that the there is no y-axis label for Figure 5, the x-axis is not labeled in Figure 9, and Figure 13 does not have a concentration for the first bar in the figure. (Office Action, at page 3, lines 17-19, at paragraph 8.)

To expedite prosecution and without acquiescing to the propriety of the objection, Applicants submit with the present Amendment replacement Figures 5, 9 and 13. Figure 5 has been amended to add the label "Densitometric Intensity" to the y-axis. Figure 9 has been amended to more clearly label the x-axis by repositioning the former x-axis labels. Figure 13 has been amended to change the x-axis label of the first bar from "Control" to "No peptide," to more clearly indicate that the first bar represents data using no peptide, *i.e.*, peptide at a concentration of zero.

Applicants believe that the objection to Figures 5, 9 and 13 has been overcome and respectfully request that the objection be withdrawn.

III. Objection to the Specification

The Office objects to the disclosure because it allegedly "has improper grammar throughout and is difficult to read," and that there are "multiple sentences throughout the disclosure that are difficult to comprehend." (Office Action, at page 4, lines 12-16, at paragraphs 9 and 10.) The Office requests appropriate correction. (Office Action, at page 4, line 17, at paragraph 10.)

To expedite prosecution and without acquiescing to the propriety of the objection, Applicants submit with the present Amendment a substitute specification in which typographical and grammatical errors have been corrected so that the language in the specification conforms to accepted English-language conventions. A substitute specification containing these changes is submitted with the present Amendment. In accordance with 37 C.F.R. § 1.125(c), both a marked-up version and a clean version of the substitute specification are provided. The substitute specification contains no new matter.

Applicants believe that the objection to the specification has been overcome and respectfully request that the objection be withdrawn.

IV. Double Patenting Rejection

Claims 19-21 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-12 of U.S. Pat. No. 7,291,594 ("594 patent"). (Office Action, at page 5, lines 17-22, at paragraph 12.)

Claims 19-21 have been cancelled, rendering the rejection moot.

With regard to new claims 24 and 25, Applicants request that the Office hold this rejection in abeyance until the remaining rejections have been resolved.

V. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 19-21 and 23 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. (Office Action, at page 5, lines 27-29, at paragraph 14.) According to the Office, claim 19 recites the limitations "the peptide" and "the physiological activity thereof," but provides insufficient antecedent basis for these limitations, while claims 20, 21 and 23, which depend on a rejected base claim, fail to cure the indefiniteness. (Office Action, at page 6, lines 1-9, at paragraphs 15-17.)

To expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have cancelled claims 19-21 and 23 and redrafted the cancelled claims as new claims 24-26, which do not recite the phrases "the peptide" and "the physiological activity thereof."

Applicants believe that new claims 24-26 in their present form particularly point out and distinctly claim the subject matter which Applicants regard as the invention and thus fully comply with 35 U.S.C. § 112, second paragraph.

Accordingly, Applicants believe that the rejection of claims 19-21 and 23 under 35 U.S.C. § 112, second paragraph, has been overcome and respectfully request that the rejection be withdrawn.

VI. Claim Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 19-21 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. (Office Action, at page 6, lines 16-20, at paragraph 19.)

Specifically, the Office states that the disclosure "does not direct one of ordinary skill in the art to the genus of GLP-1 derivatives with any modification of the peptide as currently encompassed by claim 19," and further states that the claims "are also rejected for failing to describe a genus of GLP-1 activities with the genus of modified peptides." (Office Action, at page 6, line 21, to page 7, line 2.) The Office, however, acknowledges that the disclosure describes the production of (Ser^8)-GLP-1 (7-36 amide), (Gly^8)-GLP-1 (7-36 amide), (Gln^{26}, Asn^{34})-GLP-1 (7-36 amide), (Ser^8, Gln^{26}, Asp^{34})-GLP-1 (7-36 amide), and (Ser^8, Gln^{26}, Asn^{34})-GLP-1 (7-36 amide) having trypsin and dipeptidylpeptidase IV resistance, but states that the disclosure "does not describe a representative genus of modified peptides with various physiological activities as currently encompassed by the claims." (Office Action, at page 8, lines 10-14.)

As discussed above, claims 19-21 have been cancelled, rendering the rejection moot.

New claims 24 and 25, which are redrafted forms of cancelled claims 19-21, recite GLP-1 derivatives having an amino acid sequence of a GLP-1 peptide selected from the group consisting of GLP-1(7-36), GLP-1(7-37), GLP-1(7-36 amide), and GLP-1(7-37 amide), wherein glutamine is substituted at the 26^{th} position and asparagine is substituted at the 34^{th} position in the amino acid sequence. New claim 25 recites that the GLP-1 derivative of claim 24, wherein serine or glycine is substituted at the 8^{th} position in the amino acid sequence.

Applicants believe that these new claims fully comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

Accordingly, Applicants request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

VII. Claim Rejections Under 35 U.S.C. § 102

Claims 19-21 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Dong, U.S. Pat. No. 6,903,186 ("Dong '186"). (Office Action, at page 9 paragraph 21.)

According to the Office, Dong '186 discloses peptide analogs of GLP-1 and their pharmaceutically acceptable salts, and the structure disclosed in Dong '186 encompasses a GLP-1 (7-36) that has a C-terminal amide (as in claim 1); the pending claims are drawn to modified GLP-1 derivatives, which encompass at least one or more substitutions, insertions, and/or deletions; and the peptide analogs disclosed in Dong '186 encompass such a GLP-1 derivative. (Office Action, page 9, paragraph 22.)

As discussed above, claims 19-21 have been cancelled, rendering the rejection moot with respect to these claims.

However, regarding new claims 24 and 25, which are redrafted forms of cancelled claims 19-21, Applicants believe that Dong '186 does not anticipate these new claims for at least the following reasons.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

As discussed above, claims 24 and 25 recite GLP-1 derivatives in which (1) lysine is substituted with glutamine at the 26th position, and (2) lysine is substituted with asparagine at the 34th position in the amino acid sequence. The resulting GLP-1 derivatives are resistant to trypsin digestion, and are preferably used for oral administration. The GLP-1 derivative recited in claim 25, the GLP-1 derivative is further substituted with serine at the 8th position. The resulting GLP-1 derivative is resistant to both trypsin and dipeptidyl peptidase IV. Claim 26 recites the GLP-1 derivative [Ser 8, Gln 26, Asn 34] of SEQ ID:6.

There is no disclosure or suggestion in Dong '186 of the GLP-1 derivatives recited in Applicants' pending claims (claims 24-26). Dong '186 does disclose peptide analogs of GLP-1, of Formula (I). See Dong '186, at columns 2 and 3. However, in these analogs, the amino acid at position 26 ("A26") is defined as "Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N(R^{10}-

R^{11}))-C(O) or NH-CH((CH$_2$)$_e$-X^3)-C(O)," and is not defined to include glutamine, unlike the GLP-1 derivatives recited in Applicants' present claims (claims 24-26). Similarly, the amino acid at position 34 ("A34") of the GLP-1 analogs disclosed in Dong '186 is defined as "Lys, Arg, hArg, Orn, HN-CH((CH$_2$)$_n$-N(R^{10}-R^{11}))-C(O) or NH-CH((CH$_2$)$_e$-X^3)-C(O)". Again, the amino acid at position 34 is not defined to include asparagine, unlike the GLP-1 derivatives recited in Applicants' present claims. In addition, the peptide recited in claim 1 of Dong '186, "[Aib8,35]hGLP-1(7-36)NH2," is a GLP-1 (7-36) that has a C-terminal amide, as noted by the Office, but it is not a GLP-1 derivative having glutamine at the 26th position, or asparagine at the 34th position of the amino acid sequence, again, unlike the GLP-1 derivatives currently claimed.

Thus, Dong '186 fails to disclose each and every element of the GLP-1 derivative recited in the pending claims. Because Dong '186 fails to disclose each and every element of pending claims 24 and 25, Applicants submit that it cannot anticipate these claims.

Claims 19-21 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Dong, U.S. Pat. No. 7,268,213 ("Dong '213"). (Office Action, at page 10, paragraph 23.)

According to the Office, Dong '213 discloses peptide analogs of GLP-1 (as indicated in the abstract) and the structure disclosed in Dong '213 encompasses a GLP-1 (7-36) that has a C-terminal amide (as in claim 12); the pending claims are drawn to modified GLP-1 derivatives, which encompass at least one or more substitutions, insertions, and/or deletions; and the peptide analogs disclosed in Dong '213 encompass such a GLP-1 derivative. (Office Action, page 10, paragraph 24.)

As noted above, claims 19-21 have been cancelled. Applicants submit that Dong '213 also does not anticipate new claims 24 and 25 for at least the following reasons.

Dong '213 is a continuation-in-part of Dong '186 and discloses the same GLP-1 analogs as in Dong '186. For example, none of the GLP-1 peptide analogs recited in claim 12 of Dong '213 contain glutamine at the 26th position, and/or asparagine at the 34th position in the amino acid sequence of the derivative, as required in Applicants' pending claims.

Thus, for the same reasons as discussed above for Dong '186, Dong '213 fails to disclose each and every element recited in pending claims 24 and 25. Because Dong '213 fails to disclose each and every element of the claims, Applicants submit that it also cannot anticipate these claims.

Claims 19-21 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Dong, U.S. Pat. No. 7,368,427 ("Dong '427"). (Office Action, at page 10, at paragraph 25.)

According to the Office, Dong '427 discloses peptide analogs of GLP-1 (as indicated in the abstract) and the structure disclosed in Dong '427 encompasses a GLP-1 (7-35) that has a C-terminal amide (as in claim 1); the pending claims are drawn to modified GLP-1 derivatives, which encompass at least one or more substitutions, insertions, and/or deletions; and the peptide analogs disclosed in Dong '427 encompass such a GLP-1 derivative. (Office Action, page 10, paragraph 26.)

As noted above, claims 19-21 have been cancelled and redrafted as new claims 24 and 25. For at least the following reasons, Applicants submit that Dong '427 also does not anticipate new claims 24 and 25.

Dong '427 is similar to Dong '186 and Dong '213 in that it also discloses peptide analogs of GLP-1, of Formula (I), in which the amino acid at position 26 ("A26") is not defined to include glutamine, and the amino acid at position 34 is not defined to include asparagine, unlike the GLP-1 derivatives recited in Applicants' present claims, new claims 24-26. In addition, none of the peptides recited in claim 1 of Dong '427 have glutamine at the 26th position, or asparagine at the 34th position of the amino acid sequence, again, unlike the GLP-1 derivatives currently claimed.

Thus, Dong '427 also fails to disclose each and every element of the GLP-1 derivative recited in pending claims 24 and 25, and, as a consequence, cannot anticipate these claims.

Claims 19-21 and 23 are also rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Hayashi *et al.*, JP 2002-299283, priority document of U.S. Pat. No. 7,291,594 ("Hayashi"). (Office Action, at page 10, lines 21-22, at paragraph 27.) According to the Office, Hayashi "discloses a composition that has 100% identity with the sequence disclosed as SEQ ID NO:6." (Office Action, at page 11, lines 1 and 2, at paragraph 28.)

Applicants note that Hayashi cannot be prior art under 35 U.S.C. § 102(e) because it is not an application for patent, or a patent granted on an application for patent, filed in the United States, as required under 35 U.S.C. §§ 102(e)(1) and (2). *See also* Manual of Patent Examining Procedure (MPEP), Eighth Ed. (August 2007), at § 706.02(f)(1), at page 700-29.

Applicants submit, moreover, that U.S. Pat. No. 7,291,594 (" '594 patent") – the issued U.S. patent that claims priority to Hayashi – also cannot be prior art under 35 U.S.C.

§ 102(e) because under this section, the critical reference date for the '594 patent is the date the application was filed *in the United States*. Since the '594 patent is a U.S. national phase application of an international application (PCT/JP03/13020), the critical U.S. filing date for this reference can be *no earlier than* the international filing date, October 10, 2003. Applicants note, moreover, that the critical U.S. filing date for this reference may be considered to be the international filing date of October 10, 2003 *only* if certain conditions are met, including the condition that the International Application must have been published in English. The International Application on which the '594 patent is based appears to have been published in Japanese, so that the '594 patent *may* have a critical reference date that is *later* than October 10, 2003, the international filing date. *See* Manual of Patent Examining Procedure (MPEP), Eighth Ed., (August 2007), at § 2136.03, at page 2100-93, and § 706.02(f)(1), at page 700-29.

Accordingly, under section 102(e), Applicants respectfully submit that the foreign priority date of the '594 patent – *i.e.*, October 11, 2002, the filing date of JP 2002-299283 – cannot be used to antedate Applicant's application filing date, so that neither JP 2002-299283, nor the '594 patent, can be used as prior art under 35 U.S.C. § 102(e) against the pending claims.

For the reasons give above, Applicants request that the rejections under 35 U.S.C. § 102 be withdrawn.

CONCLUSION

Based on the foregoing remarks, Applicants respectfully request that the Examiner reconsider all rejections and that they be withdrawn. Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or

informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 23, 2009 By _____

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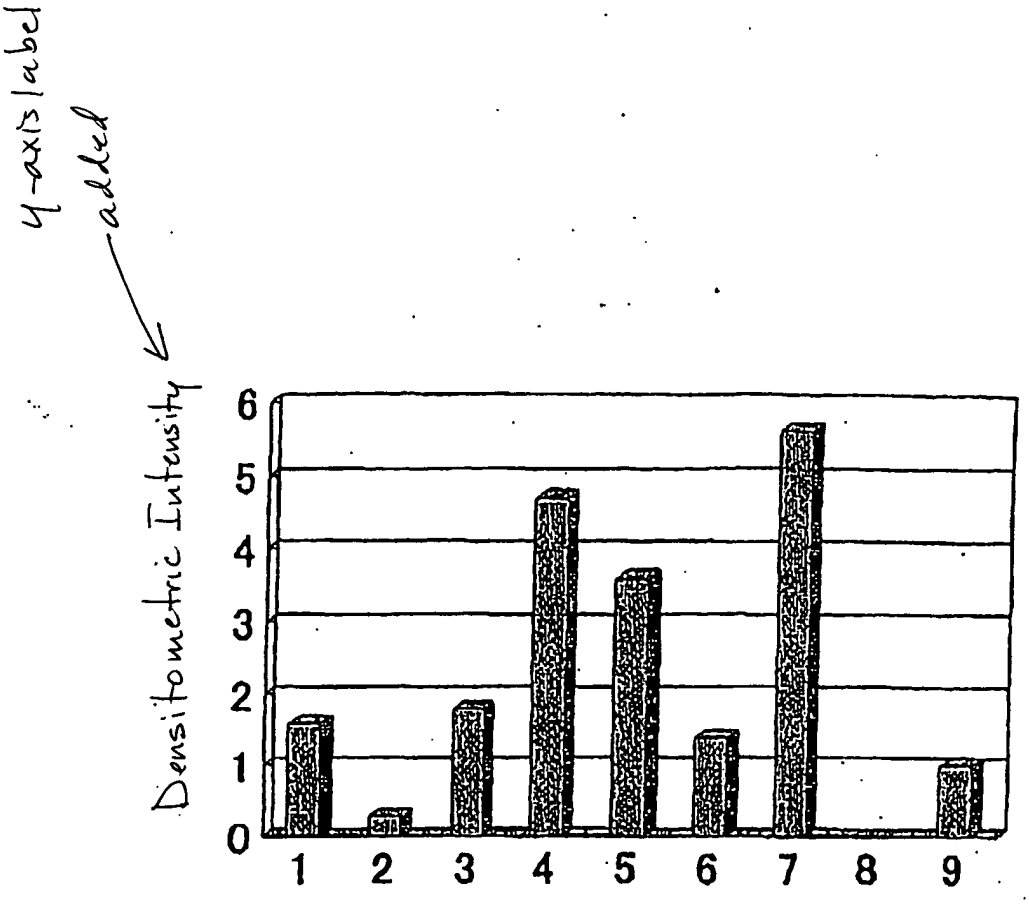
[Fig. 5]

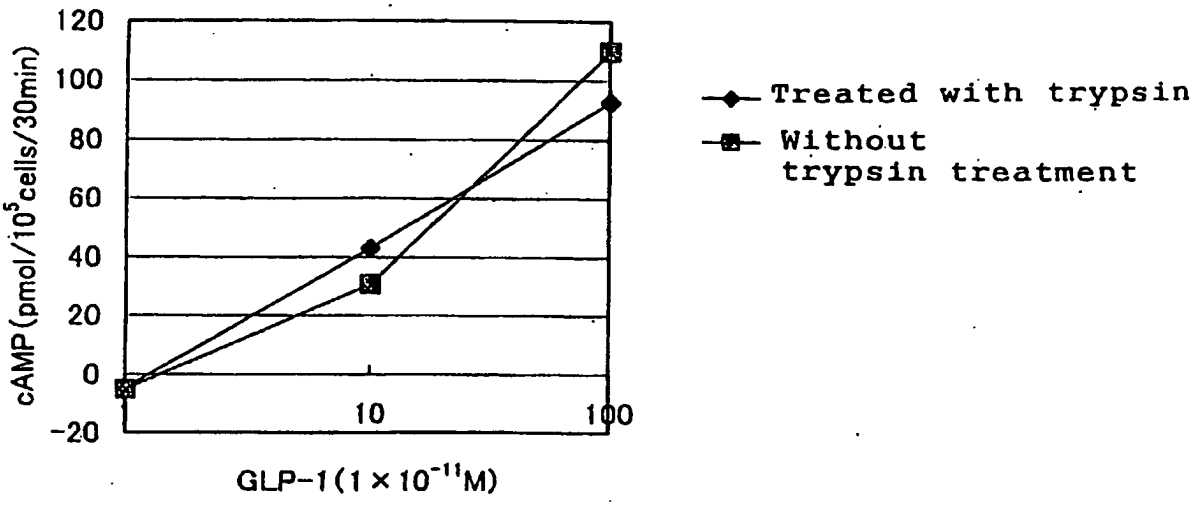


Lanes 1-7: Strains prepared in Example 1

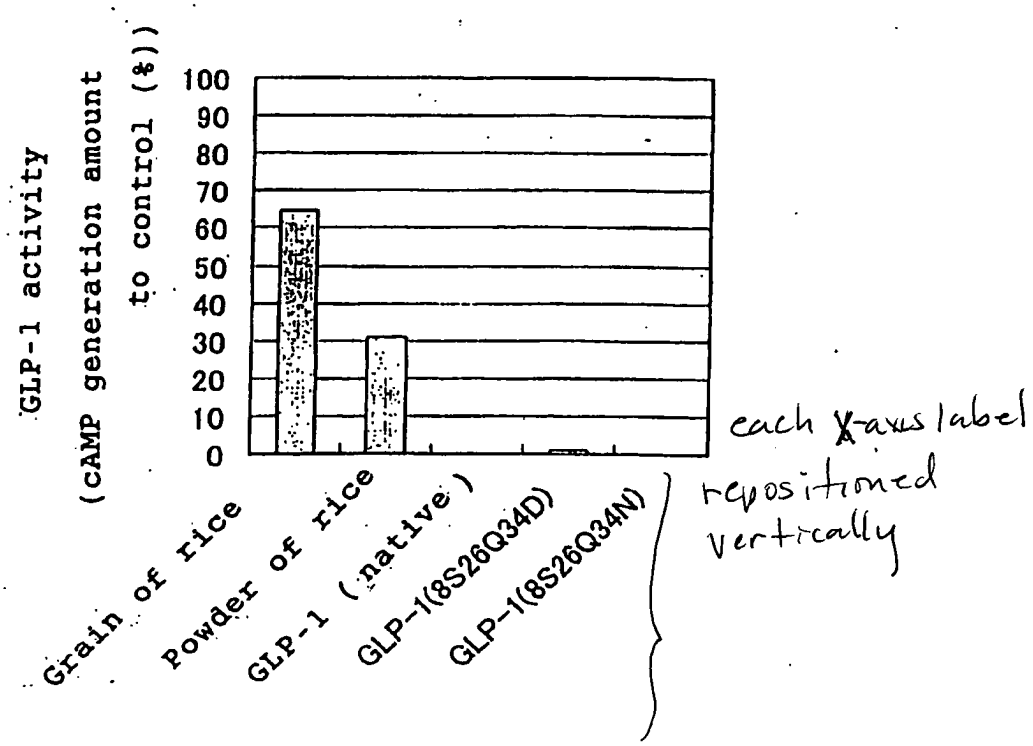
Lane 8: NIHONBARE (Non-Transformant)

Lane 9 A strain prepared in Example 1

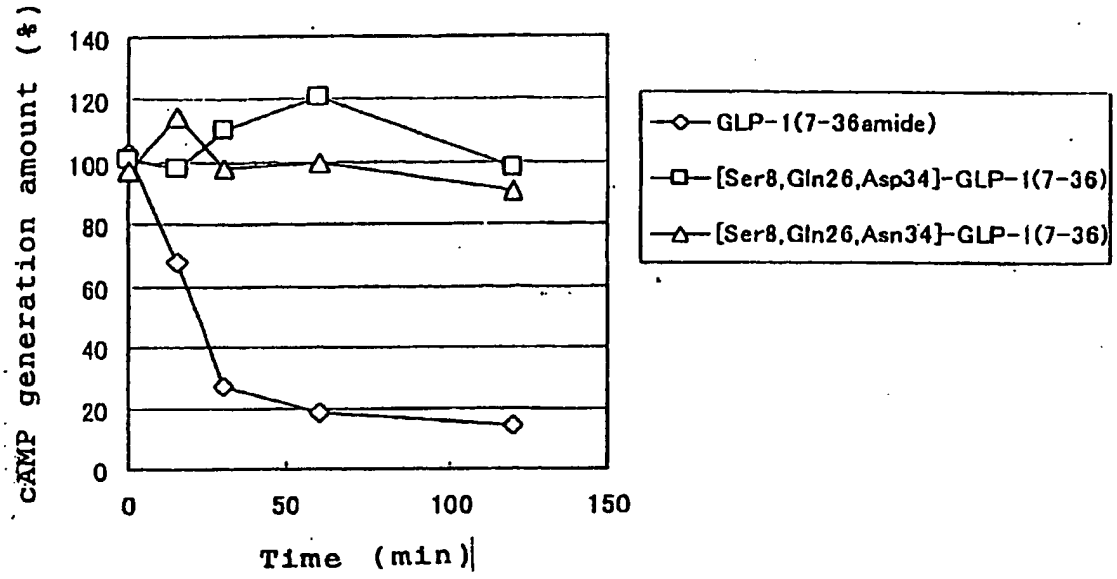
[Fig. 8]


120
100
80
60
40
20
0
-20
cAMP (pmol/10^5 cells/30min)
10
100
GLP-1 (1 × 10^-11 M)
Treated with trypsin
Without trypsin treatment

[Fig. 9]


GLP-1 activity
(cAMP generation amount to control (%))
100
90
80
70
60
50
40
30
20
10
0
Grain of rice
Powder of rice
GLP-1 (native)
GLP-1(8S26Q34D)
GLP-1(8S26Q34N)
each X-axis label repositioned vertically

[Fig. 12] **ANNOTATED DRAWINGS**



[Fig. 13]